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PYRIMIDINE DERIVATIVES FROM 1-AROYL-4,5-DIAMINO-4,5-DIHYDRO-IMIDAZOLES: A NEW RING EXPANSION

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1-Aroyl-4,5-diamino-4,5-dihydro-imidazoles (3a-f) can be prepared in good yield by reacting 1,2-diamino-ethylenes (1a-b)[1] with N-chloro-N'-aroyl-amidines (2)[2,3] (Scheme 1).

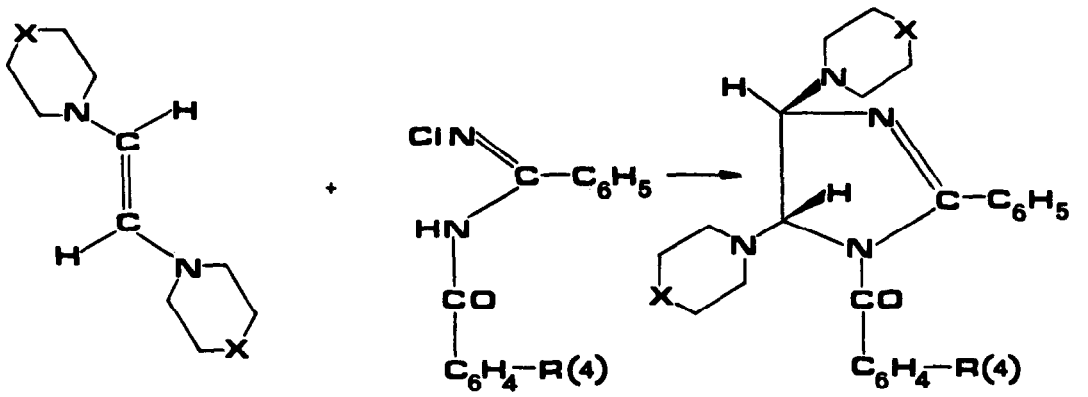
We now wish to report that imidazolines 3a-f undergo an easy ring expansion reaction to 5-aryl-3,4-diamino-pyrimidines (4a-f) (Scheme 2).

This reaction was carried out by refluxing for several hours (8-16) the imidazolines 3a-f in dry xylene. The products were obtained in 75-90% yield and were isolated by standard procedures.

Their structure was assigned on the basis of analytical (C, H, N) and spectral data (IR, ^{1}H n.m.r. and mass spectrometry).

The formation of pyrimidine derivatives 4 occurs by cyclization, followed by water elimination, of an intermediate N-aroyl-N'-(1,2-diamino-ethylidene)-amidine (5) which arises through N_1-C_5 cleavage of the imidazoline ring.

In the expansion process involving imidazoline 3a, the intermediate 5 could be isolated by stopping the reaction before completion and through column chromatography of the crude reaction mixture. N-benzoyl-N'-(1,2-dimorpholino-ethylidene)-benzamidine (yield: 35%; m.p. 137°-138°C; IR (Nujol): 1645, 1638, 1610, 1560 cm^{-1}) analyzes correctly and shows the following ^{1}H n.m.r. spectrum ($CDCl_3$, δ from TMS): 2.26 and 3.38 (two triplets, morpholine protons); 3.25 (s, $-CH_2-$); 3.49 (s, N=C-morpholine); 7.17-7.68 and 7.83-8.17 (2m, aromatic protons).

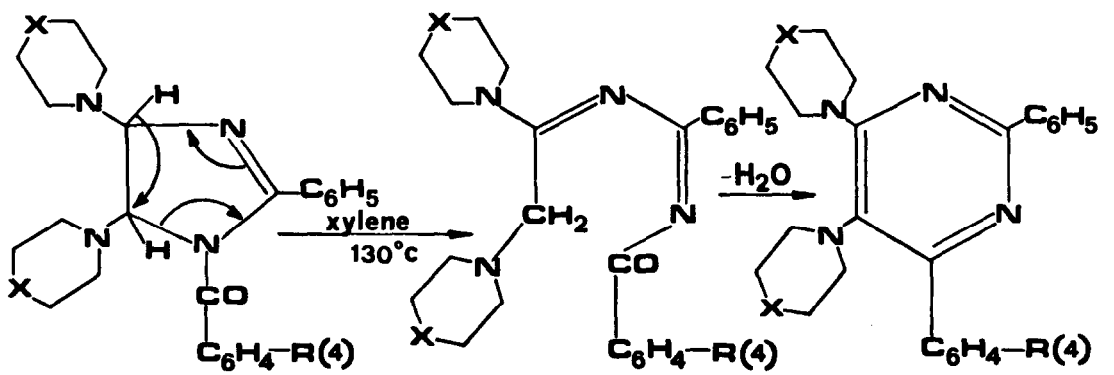


1a : x = O
1b : x = CH_2

2a-e

3a : x = O	; R = H	;	m.p. 178 °C
3b : x = O	; R = CH_3	;	m.p. 140 °C
3c : x = O	; R = F	;	m.p. 134 °C
3d : x = O	; R = Cl	;	m.p. 168 °C
3e : x = O	; R = Br	;	m.p. 178 °C
3f : x = CH_2	; R = H	;	m.p. 130 °C

SCHEME 1



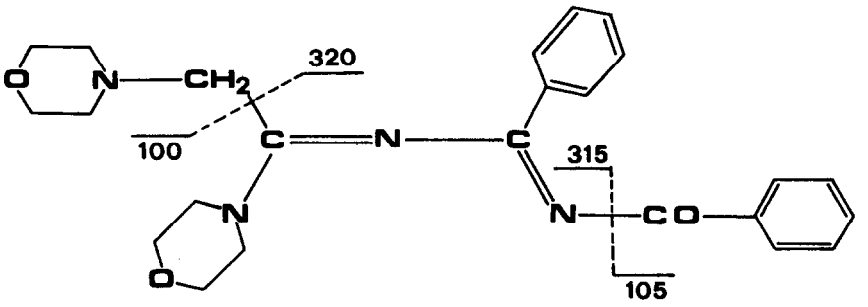
3a-f

5

4a : x = O	; R = H	;	m.p. 198 °C
4b : x = O	; R = CH_3	;	m.p. 176 °C
4c : x = O	; R = F	;	m.p. 222 °C
4d : x = O	; R = Cl	;	m.p. 222 °C
4e : x = O	; R = Br	;	m.p. 226 °C
4f : x = CH_2	; R = H	;	m.p. 136 °C

SCHEME 2

Finally its mass spectrum shows a molecular ion at 420 m/e and the following fragmentation pattern which agrees with the assigned structure[6]:

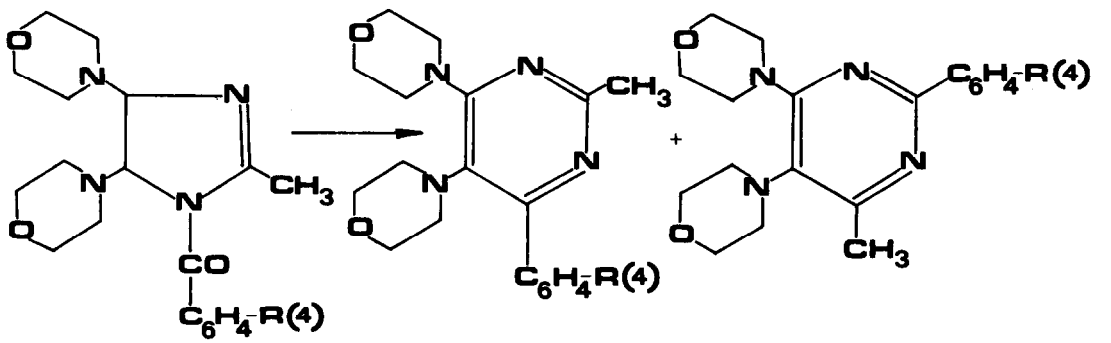


The formation of the intermediate 5 and its subsequent conversion to pyrimidines 4 could easily be shown in all cases by monitoring the reaction by thin layer chromatography.

Somewhat surprisingly, 1-aroyl-2-methyl-4,5-dimorpholino-imidazolines 3g and 3h gave under the same conditions an almost equimolar mixture of the isomeric pyrimidines (4g, 4'g and 4h, 4'h), as shown in scheme 3.

The isomers are easily distinguishable by ^{1}H n.m.r., but their mixture was found very difficult to separate completely owing to the great similarity in their physical properties. Only enriched samples (~90%) could be obtained.

At present, further work is in progress to establish more firmly the mechanism and to exploit the synthetic potential of this reaction.



3g: R = H; m.p. 151 (d) 4g: R = H 4'g: R = H
3h: R = F; m.p. 132 4h: R = F 4'h: R = F

REFERENCES AND NOTES

(1) L. Duhamel, E. Duhamel, G. Plé, Bull.Soc.Chim.Fr., 1968, 4423.

(2) This reaction which affords a new class of imidazole derivatives is being extensively studied and will be the subject of a forthcoming full paper.

(3) N-chloro-N'-aroyl-benzamidines 2a (R=H, m.p. 110°C, lit. 98°C[4]), 2b (R=CH_3, m.p. 140°C), 2c (R=F, m.p. 134°C), 2d (R=Cl, m.p. 158°-160°C), 2e (R=Br, m.p. 157°C) were prepared by the following standard procedure:

0,1 mole of N-aroyl-amidine dissolved in 100 ml of dichloromethane was reacted with 185 ml of a 10% solution of NaClO. The reaction mixture was stirred at room temperature for 1-1,5 h, the organic layer was separated, washed with 5% HCl to remove unreacted N-aroyl-benzamidine then twice with water, dried over $MgSO_4$ and freed from the solvent affording the crude N-chloro-N'-aroyl-amidines 2a-e. The crystallization from isopropylether gave the products in the pure form.

(4) T. Fuchigami and K. Odo, Bull.Soc.Chim.Japan, 1976, 3607.

(5) We would like to thank Dr. B. Gioia for helpful discussion on the analysis of mass spectra.